American Journal of Pharmacy

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(see article on Cardiac Glycosides)

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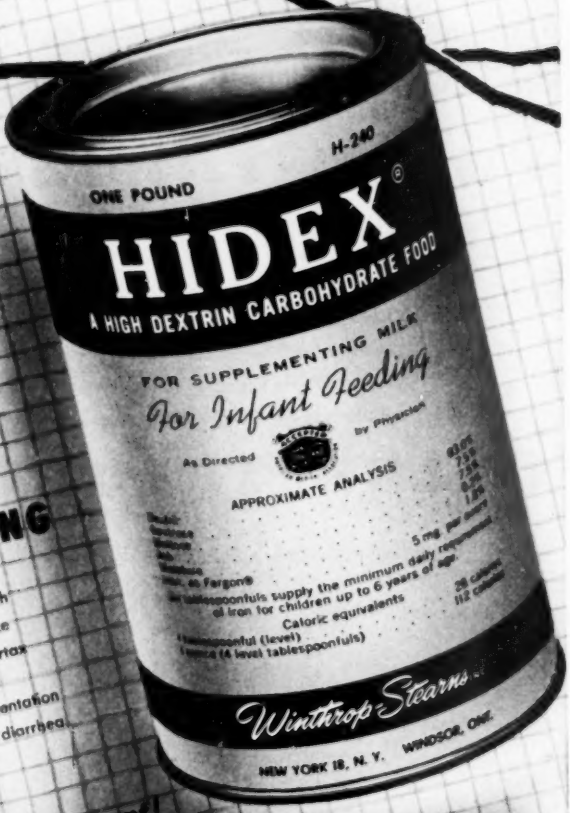

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AMERICAN JOURNAL OF PHARMACY

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EDITORIAL

PALLIATIVES—AN INCREASED NEED

WHEN one surveys the field of modern medicinals it is surprising how many drugs of the strictly palliative class are used and how their number constantly increases. Busy pharmacists and physicians rarely have time to reflect on the underlying reasons for this increased need for such drugs nor to consider how dismal are the prospects for a lessening of this need.

Before analyzing this trend it might be well to list some of those drugs which, although widely used, are strictly palliative and do not in any sense overcome the etiologic factors involved in the maladies for which they are employed. The hypnotics and stimulants are typical examples. Thousands upon thousands of people suffer from either an anxiety neurosis or chronic depression, and thus either fail to sleep though exhausted or are so depressed that all drive and enthusiasm for the day ahead is lost. The barbiturates and stimulants such as amphetamine and methamphetamine are used in unbelievable amounts, and there are millions of Americans who use these therapeutic "crutches" as a means of carrying on under conditions that might otherwise be intolerable.

The psychosomatic factors involved in peptic ulcer seem inescapable when one reviews the underlying causes of this all too common disorder. What an array of drugs we have for this! Antacids by the score, parasympatholytics by the dozen and hundreds of combinations. Yet none of these is a cure, and relapse following treatment is quite common unless, in the meantime, psychotherapy or changing environmental conditions have made a permanent cure possible.

It would be interesting to know how many patients have been subjected to surgery for appendicitis, treated for gall bladder disease, given laxatives, etc., when the underlying difficulty was pain associated with spasm induced by autonomic imbalance. Gastrointestinal spasm caused by parasympathetic over-activity is a very common condition as every physician knows, just as is the relief afforded by spasmolytics. But what causes this autonomic imbalance? Is it not the tensions and

frustations of so-called civilized life? Man, the animal, many millenia ago responded to danger with either fight or flight but modern society frowns upon both. He must not only stay upon the scene but outwardly present the appearance of unruffled calm. In polite society he is not even permitted the emotional release of swearing. Is there then any wonder that the autonomic nervous system suffers? To make matters worse, modern man is subjected to feelings of insecurity far more subtle and more intangible than those caused by the giant beasts which he once learned to conquer. By their very hidden nature, however, they are all the more difficult to cope with.

Even the relief from anxiety which a deep and abiding faith in God conveys is a surcease known and enjoyed by fewer and fewer of our people, and this in spite of statistics indicating that a majority of the people are church members.

There seems little doubt but that the classic work of Selye on the stress syndrome explains many of the diseases such as rheumatoid arthritis. If so, even cortisone may be, as it has been described, "a glorified aspirin tablet." Surely it seems that cortisone rarely does more than reduce tissue response and thus it is in a sense only a palliative. True it is nature's own way of giving protection but nature itself can be thwarted by continued stress which is contrary to the normal scheme of things.

There seems little doubt that allergy has a strong psychosomatic factor and, although such a tendency is passed by the genes to the offspring, this still does not eliminate psychosomatic factors which may act as "trigger mechanisms."

Even as simple a thing as headache is more often caused by emotional factors than otherwise and migraine is almost certainly a psychosomatic disease. Of course some will argue that changes in the bore of the cerebral blood vessels take place in migraine but this is an effect, causing pain it is true but not the underlying cause.

We might continue indefinitely listing simple complaints like constipation and dysmenorrhea and more serious diseases such as essential hypertension all of which have strong emotional factors. We might, too, consider obesity with all its sequelae as well as chronic alcoholism. Then, too, we must not overlook the millions of persons with recognized mental disease and the almost equal number who are unbalanced but not to the point that they must be confined. Statistics forecasting the future numbers of mental patients stagger the imagination.

After all this survey of psychosomatic disease and its impact on society what conclusions can be drawn? In the over-all picture things surely do not look bright for in spite of the outward prosperity which we enjoy our tensions grow worse each year. We no longer even expect a "return to normalcy", peace as once we knew it seems a thing forever past. Industrial and political strife are with us constantly. Insecurity both personal and national has been with us for over a decade. Young people when they are in their most critical and formative years can make no personal plans for marriage or careers without the constant spectre of military service standing before them. These are but a few of the conditions with which modern man is confronted and which an incessant press and radio will scarcely let him forget even momentarily.

Possibly in time a new species of man will evolve for whom the present conditions will hold no fears and provide no tensions. Just as gonococci became resistant to sulfonamides and flies are becoming resistant to DDT, so man may become tension resistant. In the meantime the use of palliative drugs should and will increase just as will those who need such treatment. Blessed indeed are they who have found a philosophy of life which meets their needs or who have found in religion a haven of refuge.

L. F. Tice

THE CARDIAC GLYCOSIDES
A Review

By George V. Rossi

Introduction

A LARGE number of naturally occurring substances, because of their glycoside structure and cardiac action, are often called the cardiac glycosides. They are characterized by the highly specific and powerful action which they exert upon the cardiac muscles. These active glycosides are found in a number of plant families; one of the most important being the family Scrophulariaceae, which includes Withering's "wayside flower", Digitalis.

> The Foxglove's leaves, with caution given,
> Another proof of favouring Heav'n
> Will happily display;
> The rapid pulse it can abate;
> The hectic flush can moderate
> And, blest by Him whose will is fate,
> May give a lengthen'd day.
>
> William Withering.

Digitalis, with its derivatives, holds an unchallenged position in the field of therapeutics. With the growing trend toward longer life expectancy, more people are reaching the age group where the degenerative type of heart disease is prevalent. This tendency is further enhancing the usefulness of digitalis.

Recently some of the concepts of digitalis therapy have undergone certain changes. With the introduction of new purified cardiac principles, the therapeutic possibilities have been enlarged. It is the purpose of this paper to present recent advances in digitalis therapy along with a a general discussion of the subject.

Chemistry

The active principles of most cardiac drugs are typical glycosidal structures, i.e.—upon hydrolysis they decompose into their genins or aglycones and split off their sugar molecules. Most of the physiologic

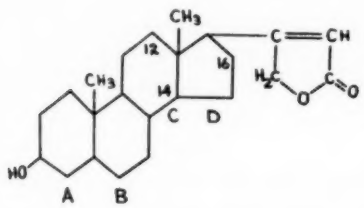
activity of the cardiac glycosides resides in the aglycone portion of the molecule. A cyclopentenophenanthrene nucleus to which is attached an unsaturated lactone ring constitutes the basic structure of the genins.

There are only minor differences chemically among the various genins. This is shown in Table I, using the formula of digitoxigenin as a pattern and the substituent hydroxyl groups at various positions.

Table I

Chemical Formulas of the Genins of the Principal Cardiac Glycosides

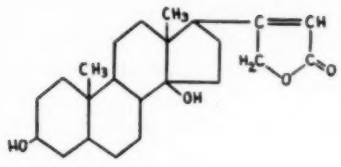
	C-12	C-14	C-16
Digitoxin		OH	
Gitoxin		OH	OH
Gitalin		OH	OH
Digoxin	OH	OH	



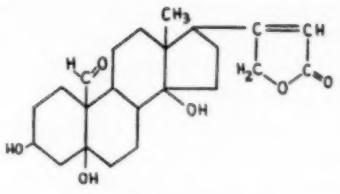
Strophanthidin differs from digitoxigenin only by virtue of a hydroxy at C-5 and an aldehyde at C-10 instead of a methyl radical. Ouabain, a crystalline glycoside obtained from Strophanthus gratus, yields the aglycone ouabagenin, the skeletal structure of which differs from digitoxigenin in having a primary alcohol group instead of methyl group on C-10, and hydroxy groups on C-7 and C-11. Scillaren-A, an important glycoside of squill, yields the aglycone scillaridin-A, which differs from the aglycones of the digitalis-strophanthus group in having an extra carbon atom. This carbon is in the lactone ring which, therefore makes scillaridin-A the intermediate link between the cardiac principles and the bile acids.

Figure I illustrates some important aglycones and their differences in structure.

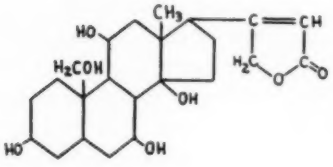
FIGURE I



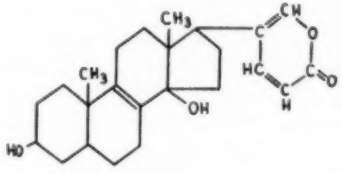
Digitoxigenin



Strophanthidin



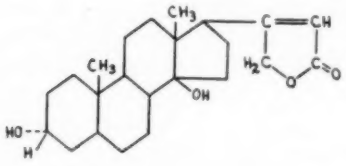
Ouabagenin



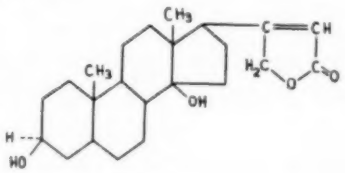
Scillaridin-A

The principal cardiotonic genins differ from each other by the stereochemical relationship of the ring structures and in the number of hydroxyl groups attached to the rings. In the genins the rings termed A and B may be either cis or trans. In steroids, when rings A and B are cis they belong to the normal series, whereas when they are trans, they are usually referred to as allo. All very active glycosides have a cis fusion of rings A and B. The hydroxyl group on position three may be either cis or trans to the carbon atom of the methyl group at position ten, although it is generally trans. Digitoxigenin is more active than thevetigenin, and these two differ only in that the hydroxyl group at C-3 of the former is trans to the methyl group at C-10, whereas in the latter the relationship is cis.

FIGURE II



Digitoxigenin



Thevetigenin

These changes modify cardiotonic activity quantitatively; the character of the response among the glycosides is essentially the same. For example, gitoxin with an additional hydroxyl group at C-16 is from 40 to 60 per cent as active as digitoxin which has only the hydroxyl group at C-14.

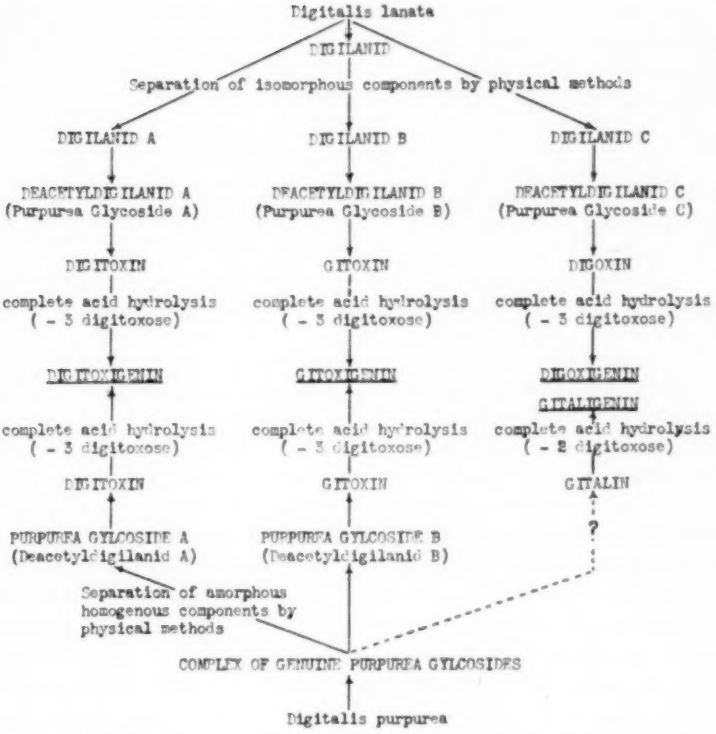
The unsaturated butyro lactone group seen in the genin is necessary for cardiotonic activity. When the double bond is removed by reduction with hydrogen the typical digitoxin action is lost. Opening of the ring similarly abolishes pharmacological activity of the molecule.

The replacement of the methyl group in the C-10 position by an aldehyde or primary alcohol group increases the activity, as they are found in the most active cardiac glycosides, such as ouabain, strophanthin and convallatoxin. It is interesting to note that acetylation of the hydroxyl group at the C-3 position in strophanthin gives a more active compound than strophanthin itself (1).

Although inactive in their pure form, the sugars when combined with aglycones increase both the potency and toxicity of the active principles. It has been observed, especially with the glycosides of squill and digitalis, that, as a rule, a lower sugar-component content will indicate a lower solubility of the compound in water. Decreased solubility may be responsible for poor absorption in the intestinal tract, and hence it is understandable that the activity of an extract decreases as the sugar content of the glycoside is reduced. The sugars are recognized as affecting the diffusion through semi-permeable membranes (cell permeability). Quantitatively the genins are less powerful and show a lesser degree of persistence in action than the unhydrolyzed glycosides. The glycosides are also distinguished by a latent period before their action becomes manifest. Digitoxigenin produces an immediate and transient slowing of the rate of the dog's heart owing to central vagal stimulation. In equimolar quantities digitoxin is devoid of this action.

The U. S. P. recognizes only Digitalis purpurea, although it recognizes two of the glycosides of Digitalis lanata, digoxin and also the native glycoside "Lanatoside C" from which digoxin is derived. The interrelationship between Digitalis purpurea and Digitalis lanata glycosides are given in Figure III.

FIGURE III



Interrelationship of the Gylcosides of *Digitalis lanata* and *Digitalis purpurea.*

Stoll demonstrated that the glycosides digitoxin and gitoxin, for a long time known as pure, active principles of Digitalis purpurea, are actually degradation products of the compounds as they exist in the natural state (2). These natural glycosides are identical with those in Digitalis lanata with only one exception: They lack the acetyl group and are therefore known as deacetyl lanatosides A and B (yielding with the loss of glucose on hydrolysis the glycosides digitoxin and gitoxin respectively). The natural glycosides for gitalin in Digitalis purpurea has not yet been isolated. No counterpart of the glycoside gitalin can be found in Digitalis lanata, on the other hand the latter contains a glycoside, digoxin, not found in ordinary digitalis.

Physiology

It would seem appropriate at this time, before considering the pharmacology of drugs which are of value in the treatment of heart disease, to review briefly the special characteristics of cardiac tissue which may be influenced by drugs, and to recall briefly a few of the common pathologic conditions which respond to drug therapy.

Heart muscle possesses those characteristics of all muscle tissue, i.e.—tonicity, conductivity, contractility, irritability, and, in addition, cardiac tissue possesses the intrinsic power of rhythmic contraction. The capacity of the heart to contract rhythmically is an inherent property of the myocardium. It is independent of the nerve supply to the heart and continues after severance of the extrinsic nerves or their blockade with drugs (3).

Initiation and Transmission of the Heartbeat—The wave of cardiac excitation begins at the sino-auricular (S-A) node, usually referred to as the "pacemaker", and passes through the auricles and the ventricles. The impulse is transmitted to the auricular-ventricular (A-V) node and across the inter-auricular septum to the left auricle through the muscular tissue. It spreads at practically equal rates in all directions: There is no tract of specialized tissue offering a pathway of "least resistance" to the A-V node. From the A-V node the impulse spreads through special tissue, known as the Bundle of His, to the ventricles. The Bundle divides into a right and left branch, each supplying the corresponding ventricle. These divisions pass downwards and are obscured beneath the endocardium of the septum. The excitatory wave is conducted through the ventricular walls from the Bundle of His by means of the Purkinje Fibers, which form a network of interlacing filaments passing directly to the cardiac muscle fibers (4).

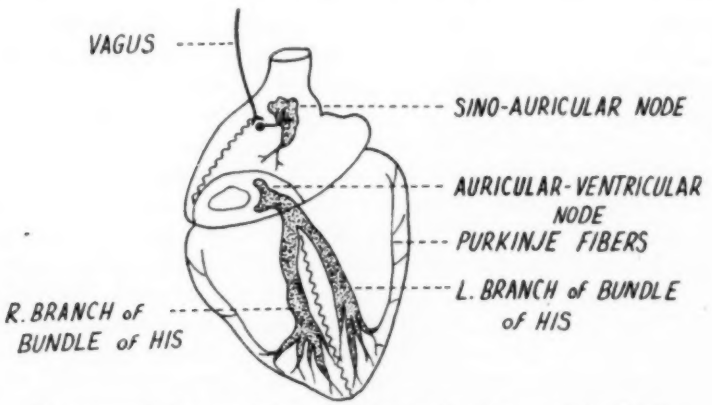
The wave of excitation which passes over the heart initiates the auricular and ventricular beats. After the retreat of the electrical impulse the myocardium enjoys a refractory period. During this period in which the muscle is undergoing metabolic and physical changes preparing itself for the next systole the heart is refractory to stimuli.

Nervous Control of the Heart—The heart is supplied with nerves which, while they do not initiate the heartbeat, influence it in various ways according to the needs of the body: (a) The vagus nerve (para-

sympathetic). The vagus nerve is the cardiac inhibitor. Vagal stimulation produces cardiac slowing and ultimately cardiac arrest. In mammals the vagus nerve exerts its slowing effect upon stimulation by its action on the auricles and junctional tissue. The vagus nerve has no direct action on the ventricles. (b) The cardiac-accelerator nerve (sympathetic). By stimulating the cardiac-accelerator nerve the heart rate is increased, the force of contraction of the auricles and ventricles is increased, and the conduction from the auricle to the ventricle is accelerated. (c) Afferent vagal fibers. The receptors of these fibers lie in the auricular tissue and the aortic arch. An increase in the blood returned to the right auricle by the vena cavae distends the auricle, resulting in stimulation of the vagal receptors. The afferent vagal fibers carry impulses to the vagal center which produces efferent vagal depression and cardiac acceleration. The increase in heart rate induced by a rise in the pressure of the blood entering the right auricle is known, after its discoverer, as the Bainbridge Reflex. Through this reflex the heart automatically adjusts its rate in accordance with the volume of blood in the venous return.

The carotid sinus functions in a manner similar to the afferent vagus fibers. Pressure in the sinus caused by an increase in blood pressure reflexly causes cardiac inhibition through the vagus center and a subsequent fall in blood pressure.

FIGURE IV



Diagrammatic Representation of the Conduction System of the Heart

Through reciprocal action of the cardiac centers a balanced mechanism is established, enabling the heart to meet extra strain that may be thrown upon it. As long as the heart can do this it remains compensated. Many conditions, however, decrease the efficiency of the heart muscle and force it to call more and more upon its reserve energy. When the heart is unable to pump sufficient blood into the systemic circulation, the condition is known as myocardial insufficiency. The patient develops cardiac decompensation. In most instances signs of venous congestion—increased venous pressure, capillary engorgement, edema, etc., appear; the term congestive heart failure being then applied.

Circulatory failure may be precipitated by the reduction in the myocardial reserve of the heart which has been working against some inordinate resistance or at a mechanical disadvantage; or it may be the result of an increase in the burden of a heart whose reserve has already been lowered by myocardial disease. Among the commoner causes are: (a) Infections, the increased cardiac work resulting from the rise in metabolic rate caused by fever. (b) Excessive muscular effort. (c) Chronic pulmonary conditions, emphysema, bronchitis, etc., accompanied by excessive coughing. (d) Pregnancy. (e) Rapid heart action, e.g., auricular fibrillation, paroxysmal tachycardia. (f) Hyperthyroidism.

Pharmacology

The pharmacological properties and indications for use of the cardiac glycosides are in all essential aspects identical for the group as a whole. The broader aspects will be listed in the discussion of the pharmacology and clinical application of digitalis; whatever differences may be found between the chemically pure glycosides and digitalis will be considered in the individual reviews.

The maintenance of circulation entails a complex interplay of a number of physiological factors. The heart rate, cardiac output as measured by stroke and minute volumes, peripheral resistance, and blood pressure are so closely interrelated that the alteration in any one of these variables usually affects, directly or reflexly, any one or all of the others. This makes the appraisal of the action of a therapeutic agent on each one of them separately a difficult matter. However certain aspects of the pharmacological properties of digitalis have been elucidated, while others await further investigation (5).

Action of Digitalis on Heart Muscle—There is no question that cardiac muscle is much more sensitive to cardiac glycosides than are other muscles of the body. It appears that the glycosides enter the cell protoplasm and are there split to release the active aglycones. The nature of the biochemical action of digitalis on the heart muscle is not clearly understood. One theory proposed that by virtue of some chemical and physical processes digitalis increases the ability of the muscle fibers to swell, thus leading to stronger contractions and greater facility in relaxation. It has been suggested that improvement in cardiac function is affected by intracellular sodium-potassium exchange. In this connection it may be remembered that the potassium ion is known to be necessary for normal cardiac function. Still another explanation is that the cardiac glycoside and cholesterin combine to form a cholesteride which is utilized in this form. How the latter cause such remarkable changes in muscular contraction is a mystery, therefore the following description is limited to observed facts rather than to an explanation of how digitalis causes the heart muscle to beat more forcibly.

Digitalis acts on the myocardium to increase the force of systolic contraction and the mechanical efficiency of the heart muscle. Other actions of digitalis are secondary and not indispensable. With increased contraction the ventricles empty more completely; the heart is rendered capable of caring for an increased venous return, and if venous pressure is high due to congestive failure, it is lowered toward normal. The diastolic filling may be increased, especially if the rate of the heart is slowed. Not only is the force of systole improved, but the length of time in each cardiac cycle occupied by systole is shortened. This naturally allows more time for the heart muscle to rest and for the ventricle to fill.

The binding of glycosides by blood proteins has been extensively studied (6). Considerable differences exist among the various glycosides. For example, glycosides such as lanatoside A and digitoxin are very strongly bound, while lanatoside B and scillaren A are only fairly strongly bound; K-strophanthoside and lanatoside C are practically not bound at all by the blood serum. The inhibition of the glycosides is not due to a destruction of the drug, but can be better explained by assuming that an inactive compound is formed between the glycoside and certain components of the blood. It is felt that the protein-glycoside binding influences the rapidity with which the drug

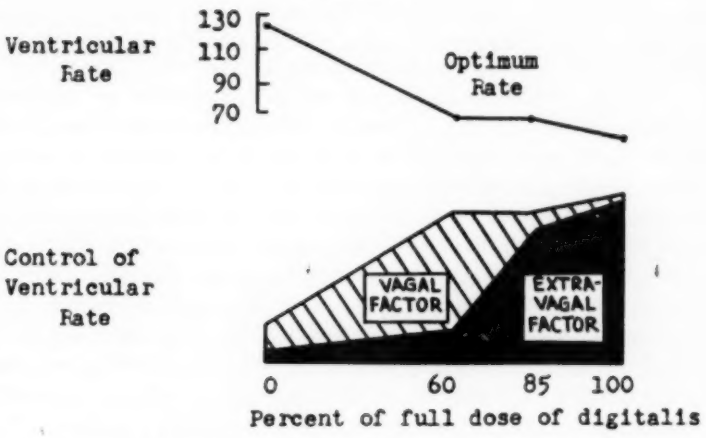
acts, and the delayed onset of action of some glycosides can be explained by this adsorption phenomenon.

Whatever may be the biochemical mechanism of digitalis action on the myocardium, the fact remains that the drug enhances the force of systolic contraction of the diseased and dilated heart. This improvement in circulation is reflected in an alteration of a number of physiologic functions as cardiac rate and output now to be considered.

Heart Rate—The original observations on the effect of digitalis in auricular fibrillation led to the general impression that slowing of the cardiac rate was the cardinal property of the drug. This action was ascribed to the production of A-V block. It was thought that ventricular slowing was primarily responsible for the restoration of compensation and that fibrillation of the auricles constituted practically the only indication for digitalis therapy. That digitalis is chiefly effective in congestive failure regardless of rhythm has been clearly demonstrated. In this connection, the view that the direct action of the glycoside on the myocardium rather than the cardiac slowing *per se* is responsible for the relief of congestive failure has gained prominence. The slowing of the heart rate is thus regarded by many as the effect rather than the cause of recovered compensation.

In animals digitalis can be shown definitely to decrease the rate of the heart. This action is mediated in large part through the vagus nerves because it is not so manifest after atropinization or vagotomy and is not so prominent in isolated hearts. The manner in which the vagus is stimulated by digitalis is not completely clear. Gold and his associates have analyzed the relative importance of the vagal and extra-vagal components of the digitalis-induced slowing of the ventricular rate in patients with auricular fibrillation (*7*). The showing produced by small doses of digitalis could largely be attributed to vagal stimulation in that the cardiac rate could be increased by large doses of atropine. This vagal slowing was interpreted as being largely reflex in nature and due to restoration of myocardial compensation. After full doses of digitalis, however, atropine no longer was capable of increasing cardiac rate, and the ventricular slowing was clearly due to extra-vagal actions.

FIGURE V



Mechanism by Which Digitalis Slows the Ventricular Rate in Patients with Auricular Fibrillation

Mechanism of Digitalis action on the Heart Rate—(a) Effect on the cardiac pacemaker: If therapeutic amounts of digitalis affect the S-A node directly or through vagal stimulation, this action is not prominent. Even in patients with hyperthyroidism or infection, digitalis in full doses has little restraining action on the rate of pacemaker discharge. Toxic doses, however, affect the S-A node directly. (b) Effect on the conduction system: Conduction between the auricle and ventricle is slowed by clinical doses of digitalis. The slowing of conduction, which is partly vagal in origin but mainly a direct action of the drug on the conduction bundle, occurs in normal as well as in decompensated hearts. It must not be forgotten that the Bundle of His is composed of muscle tissue which shares the same cardiotonic effect of digitalis as does the remainder of the myocardium. When cardiac muscle contracts more strongly, its refractory period is increased and its rate of conduction is decreased. With toxic amounts of digitalis, degrees of A-V block may occur which so interfere with the transmission of auricular impulses that partial heart block or complete auriculoventricular dissociation may result. (c) Cardiac slowing in auricular fibrillation: In this condition too many auricular impulses manage to reach the ventricle which thus beats rapidly and

irregularly. With digitalis the ventricular rate is often reduced to an optimal level. Both the vagal factor and the direct actions of digitalis on the conduction system cooperate to block auricular impulses (8).

Cardiac Output—It is important to realize that the influence of digitalis in health is different from that in disease. In normal hearts cardiac output is definitely diminished in digitalis. This is due to the fact that the heart is decreased below its optimal size by the direct cardiotonic action of the drug. The capacity of the ventricle is reduced and hence the stroke volume is lessened. In failing hearts, however, cardiac output is increased by digitalis. As is the case in the normal heart, cardiac size is reduced, but this change is from a dilated inefficient ventricle toward a more normal and efficient one. As a result of a more optimal diastolic size, stroke volume is increased and systolic ejection of blood is more forceful and complete. The increased stroke volume more than compensates for the slowing action of digitalis, with the result that both the cardiac output per minute and per beat is enhanced.

Venous Pressure—Increase in cardiac output results in a lowering of venous pressure, if initially elevated. With augmented efficiency of the heart as a pump, the blood is propelled more effectively, the heart chambers are emptied more completely, and the venous stasis is relieved.

Blood Pressure—In normal hearts the rise in systolic pressure is insignificant, if at all present, and when present is very transient. As the cardiac output in normal persons is not increased by digitalis (and even may be actually decreased), this slight rise in blood pressure can be explained by some degree of peripheral vasoconstriction. However, only when administered in toxic doses has digitalis been found to exert a definite vasoconstricting effect leading to a rather appreciable rise in systolic blood pressure. The results of therapeutic doses of digitalis upon blood pressure in patients with heart failure is quite variable. If there is tendency for the systolic pressure to rise, this may be more than compensated for by reflex adjustments. The rise is usually non-significant and does not reach a higher level than that which is customary for the patient under normal circumstances.

From this it clearly follows that hypertension does not constitute a contraindication to the administration of the drug.

Diuretic Action—The main cause of edema and serous effusion in congestive heart failure is the increase in hydrostatic pressure in the venous ends of capillaries, preventing the normal resorption of extracellular fluid. With improvement in circulation the venous pressure is relieved. As a result, the hydrostatic pressure in the venous ends of the capillaries is returned to normal, allowing resorption of the edema fluid back into the circulation. At the same time the renal function is also improved by relief of vascular congestion in the kidneys, and the excess fluid absorbed back into the circulation now easily finds its way through the cleared glomerular tufts into the excretory units of the kidneys. Many cardiac patients require additional and specific measures to promote diuresis; the employment of mercurial diuretics often becomes imperative.

Effect on the Clotting Mechanism—It has recently been demonstrated that digitalis affects the clotting mechanism. It was suggested that this effect of the drug might be a component in the cause of coronary thrombosis occurring in digitalized patients (9). The mechanism of this action has not been elucidated. Several possibilities have been suggested: Digitalis may have thromboplastic properties; it may mobilize prothrombin from the liver, or even increase thrombin or fibrinogen. In auricular fibrillation the factor of auricular stasis adds to the hazard of thrombosis.

Toxicity—The toxic effects of digitalis are largely extensions of the therapeutic actions of the drug. For this reason, a "non-toxic" digitalis preparation does not exist. A preparation which will not cause digitalis poisoning when given in excess is also one which will not exert any therapeutic effect.

Digitalis poisoning, as usually encountered today, is due to the continued ingestion of the drug in amounts greater than are destroyed or eliminated. The glycoside accumulates in the body and perhaps especially in the heart muscle. Anorexia, nausea and vomiting are among the earliest evidences of overdosage. Experimental evidence points to the fact that the vomiting is reflex in origin and arises neither from irritation of the alimentary tract nor from direct stimu-

lation of the medulla. At this stage in our knowledge it is believed that the drug excites the central vomiting mechanism only through afferent stimuli arising from the over-digitalized heart.

Probably the most frequent cardiac effect of digitalis overdosage is the occurrence of extrasystoles. These originate most commonly in the ventricle but can arise from the auricle. The ectopic beats are caused by the increased irritability of the myocardium produced by excessive amounts of digitalis. Ventricular fibrillation is the commonest cause of death from digitalis poisoning. It is particularly likely to occur from the injudicious use of large intravenous doses of the cardiac glycosides.

Available Preparations

All digitalis-like drugs manifest the same type of cardiac activity and it has not been conclusively demonstrated that the various digitalis fractions have great clinical advantage over the galenical preparations. The skillful use of the relatively inexpensive tincture or powdered leaf proves satisfactory in the great majority of cardiac patients. Purified proprietary preparations of digitalis leaf include DIGALEN (Hoffman-LaRoche), DIGIFOLIN (Ciba), and DIGITAN (Merck). They are available as tablets and solution for oral use, and ampules for injection (10).

Digitoxin—Digitoxin, the chief active glycoside of Digitalis purpurea, is available in crystalline form sufficiently pure to be administered by weight. It is almost completely absorbed from the intestinal tract and a given dose produces practically the same therapeutic effect whether given by mouth or by vein. The full digitalizing effect following oral administration occurs as quickly as when the same dose is administered intravenously; thus intravenous administration is unnecessary in the average patient. Many authors have stated that, "because of its slow dissipation and the possibility of prolonged and severe toxicity, digitoxin is not the glycoside of choice." It is available as tablets and solution for injection from many manufacturers under its official title and as PURODIGIN (Wyeth) and DIGITALINE NATIVELLE (Varick).

Gitalin—The commercial gitalin is an amorphous substance and probably not a chemical individual. The activity, duration of action and toxicity closely parallels that observed with digitalis. It is marketed as tablets GITALIN, Amorphous (Rare).

Digilanid—Digilanid is a preparation of Digitalis lanata, of constant composition in contrast to official digitalis. It represents a mixture of pure natural glycosides of the lanata leaf, standardized gravimetrically. The digilanid mixture introduced into clinical practice has been found to contain about 47 per cent lanatoside A, 16 per cent lanatoside B and 37 per cent lanatoside C. Therapeutically digilanid appears to have the advantage over most purpurea preparations of being crystalline pure, well and quickly absorbed from the grastrointestinal tract, non-irritating to the stomach and chemically stable. It acts somewhat more rapidly than Digitalis purpurea, but is less cumulative. Marketed by Sandoz as DIGILANID, tablets and solution for injection.

Lanatoside C—Lanatoside C, which has no close chemical counterpart in ordinary digitalis, is not only the most active of the three Lanatosides but also possesses a wider therapeutic range. Lanatoside C has a strophanthin-like effect due to its rapidity of action and somewhat weaker cumulative ability. At the same time it has the advantage over strophanthin because it is effective orally.

In the last few years the use of Lanatoside C has been acclaimed a very convenient and highly satisfactory way to rapidly digitalize a patient. Objective improvement occurred two to four hours after intravenous administration and forty-eight hours after the initial oral dose. Maintenance is effected with oral doses without changing to another preparation, as would be necessary in the case of strophanthin. Available as tablets and solution for injection as CEDILANID (Sandoz).

Digoxin—Digoxin is derived by hydrolytic cleavage from the natural glycoside, Lanatoside C. Its action is manifest usually within a few hours when administered orally and within a few minutes when given intravenously. It is not completely absorbed by the oral route, but due to its more rapid elimination than digitoxin, it is thought that its effects are more easily controlled. Marketed as tabloids and solution for injection as DIGOXIN (Burroughs Wellcome).

Strophanthin—Strophanthin is a glucoside or mixture of glucosides obtained from the seeds of Strophanthus Kombe or of Strophanthus hispidus. The drug is of particular value where rapid digitalization may be desirable. The pharmacologic properties of strophanthin and digitalis are practically identical, except that strophanthin acts more promptly and is eliminated with greater speed. Its absorption is so uncertain that oral administration is not advisable. Ampuls of STROPHANTHIN K are available from Abbott. The amorphous fraction, k-strophanthoside is marketed under the commercial name of STROPHOSID (Sandoz).

Ouabain—Ouabain, a glycoside obtained from Strophanthus gratus, has qualitatively identical actions with the official strophanthin, but the crystallized ouabain is uniform while strophanthin, being amorphous, varies from lot to lot. Ouabain is not available orally. It is available under its official title from many manufacturers.

Squill—The glycosides of squill are effective cardiac remedies. Their action on the heart muscle and the conducting system is similar to that of digitalis and other cardio-active principles. However, they do not offer any advantage over digitalis. Their clinical application may be reserved for those patients in whom digitalis induces nausea, vomiting or diarrhea. A mixture of two natural glycosides occurring in fresh squill, in the proportions which they exist in the crude drug is marketed as SCILLAREN (Sandoz) in tablet form and solutions for oral and parenteral use. The amorphous fraction is marketed as SCILLAREN-B (Sandoz), intended for intravenous administration when immediate action is indicated.

There are three important considerations in the choice of a satisfactory digitalis preparation: (a) The latent period before action, (b) The rate of dissipation, (c) The rate and completeness of absorption. For acutely decompensated patients, intravenous injection of strophanthin or ouabain is indicated. For routine use the other cardiac glycosides are employed, depending on the preference and experience of the attending physician.

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EFFECT OF POLYVINYLPYRROLIDONE (PVP) ON PHARMACOLOGICAL ACTIVITY

By J. N. Moss, Robert Brendel, J. M. Beiler and Gustav J. Martin *

POLYVINYLPYRROLIDONE (PVP) was originally introduced as a plasma substitute (1) and has also been shown to have the property of combining with certain substances in the blood and thus acting as a transport vehicle (2,3,4). Reports have indicated that this property may be of clinical value in two ways. Since PVP is excreted through the kidneys, it has been reported to function as a detoxifying agent (5) on the basis that it will cause elimination through the kidneys of substances which are not normally excreted in this manner. PVP has been reported also to increase the duration of action of several pharmacological agents, such as novocaine (6), insulin (7) and penicillin (8). This effect is presumably due to a slowing of absorption and metabolism because of the formation of a molecular complex.

The therapeutic utility of an agent with properties such as those described above is obvious. It was therefore decided to investigate the effect of PVP on the toxicity and general pharmacological properties of compounds of several different types, in order to determine to some extent how widespread an application this material might have as an adjuvant in therapy.

Experimental

Mice were used for toxicity testing. PVP was administered intraperitoneally as 0.5 cc. of a 20% solution. Blood pressure work was done on pentobarbitalized cats. Here PVP was administered intravenously in the form of a 2.7% solution.

Five compounds were investigated. Sodium nitroprusside and potassium thiocyanate were examples of inorganic salts. Both of these compounds have been used as hypotensive agents. They have been reported to have some effectiveness in this connection, but this has been largely vitiated by their toxicity. Epinephrine, a metabolite with a powerful pressor action, was also tested, as was 9-amino-

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acridine, an effective antiseptic with considerable toxicity. Sodium pentobarbital was the final compound in the series.

Results and Discussion

Nitroprusside toxicity was lowered when the compound was given in combination with PVP intraperitoneally. However, when the PVP was given from 5 to 45 minutes before the nitroprusside there was no protection. Similarly, when nitroprusside was given orally and the PVP intraperitoneally, there was no effect. In chronic testing, with the nitroprusside given orally and the PVP intraperitoneally, no protection was obtained.

Polyvinylpyrrolidone therefore does not protect the organism from the toxicity of sodium nitroprusside, and does not decrease the toxicity of its breakdown products, as evidenced by the results of the chronic testing. The lowering of acute toxicity noted on simultaneous intraperitoneal administration of the two materials is presumably due to a decrease in the rate of absorption of the nitroprusside, probably because of a combination that reduces the rate of absorption of the nitroprusside to that of the PVP. That such a combination does occur is shown by the results obtained on blood pressure lowering. A dose of 10 mcg. of nitroprusside intravenously in cats caused a 40 mm. drop in blood pressure. When this dose was given simultaneously with 10 cc. of 2.7% PVP solution there was no effect. The PVP in this instance causes an inactivation of the nitroprusside, even when it is given by the intravenous route.

The chronic toxicity of thiocyanate was increased by PVP when the thiocyanate was given orally. Since the toxic effect of thiocyanate is largely cumulative, it is apparent that the renal clearance is not increased by PVP and may actually be decreased. An alternative explanation is that the PVP may increase the permeability of tissues to the thiocyanate, or act as a storage medium in the tissues, and thus cause the observed increase in toxicity.

PVP had no effect on the acute toxicity of 9-aminoacridine or epinephrine, whether the toxic doses were given by the same route as the PVP (intraperitoneally) or intravenously. There was, however, a definite effect on the toxicity of pentobarbital. When PVP was administered simultaneously with minimum lethal doses of pentobarbital toxicity was decreased.

TABLE I

EFFECT OF PVP ON TOXICITY OF PENTOBARBITAL

Dose of 20% PVP	Dose of Pentobarbital	Survivals/Treated
0 cc.	150 mg/K	4/8
0.5 cc.	150 mg/K	8/8
0 cc.	175 mg/K	1/8
0.5 cc.	175 mg/K	6/8

The anesthetic effect of the pentobarbital was reduced as well by combination with PVP.

TABLE II

EFFECT OF PVP ON ANESTHETIC EFFECT OF PENTOBARBITAL

Dose of 20% PVP	Dose of Pentobarbital	Duration of Anesthesia (Min.)
0 cc.	100 mg/K	36
0.5 cc.	100 mg/K	24
0 cc.	50 mg/K	20
0.5 cc.	50 mg/K	12

Since renal clearance is not an important factor in pentobarbital detoxication the effect of the PVP is probably to slow up the absorption of the barbiturate. It is interesting to consider that PVP has been reported to show the same effect with phenobarbital, but not with barbital (9). On the other hand increases in duration of anesthesia due to PVP have been reported with Evipal (10) and Pentothal (11).

These reports point up the fact that the effect of PVP as an adjuvant in therapy is not predictable, even when applied within a group of related compounds like the barbiturates. Reductions in toxicity may be associated with decreased therapeutic effectiveness, as in the cases of nitroprusside and pentobarbital. Actual increase in toxicity, as in the case of thiocyanate, may be obtained. It is therefore apparent that care must be exercised in the use of PVP as an adjuvant in therapy, and that this use cannot be considered to be

general, but must be examined carefully for discrete substances, even when they are closely related chemically.

Summary

The effect of PVP on the toxicity and physiological actions of a group of compounds of different chemical structures has been investigated.

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ACTION OF NICOTINIC ACID ON CARBOHYDRATE METABOLISM IN DIABETICS

By Saul Caspe, Benjamin Davidson, and Samuel Marsh *

VILTER, Vilter and Spies (1) showed that blood of a diabetic patient lacks CO I which differentiates it from normal blood or the blood of the same diabetic patient treated with nicotinic acid. The effect of nicotinic acid in this respect is due to its component role in the synthesis of CO I. This work stimulated interest in nicotinic acid, its possible therapeutic value and its mechanism of action. Göbell (2) and (3) found that nicotinic acid amide lowers blood sugar and creatine and intensifies the action of both adrenaline and insulin. F. J. Neuwahl (4) confirmed the action of nicotinic acid on normal persons and found that it potentiates the action of insulin. In his clinical study of the value of nicotinic acid in the treatment of 12 older diabetics he reports that a cure was observed in three cases. The patients received as much as four or five enteric coated tablets of 500 mg. niacinamide daily and decided improvement was noted within a few days. After the first week of treatment, the dosage was reduced to three tablets of 100 mg. niacinamide daily. These tests were run for approximately fifteen days. The other nine patients showed that their blood sugars could be maintained fairly normal by this treatment even without insulin. There has not been any confirmation of Neuwahl's experience reported since 1943. Although his astounding results were limited to a few cases, we directed our attention to a close study of his thesis. The work of Gabler and Mathies (5) added weight to this thesis for they reported that depancreatized dogs with constant food and insulin intake showed marked glycosuria following and resulting from the deficiency of "B" complex vitamins. Since they further demonstrated the loss of these diabetic symptoms upon the addition of B_1, B_2, nicotinic acid and pyridoxine, we were induced to repeat the Neuwahl clinical experiment.

Our plan was to try nicotinic acid amide on diabetics and to compare it with the effects of CO I upon similar cases. In this way we hoped to explore the role of nicotinic acid amide by also studying the action of the end product which it forms and which is at least one factor recognized as deficient in diabetics.

* Good Samaritan Dispensary, New York City.

A batch of 500 mg. enteric coated niacinamide (N. A. A.) [a] tablets was made; each contained a minimum of sugar, 0.1 grain of gelatine and 0.1 grain of calcium stearate as a lubricating agent. The enteric coating consisted of cellulose acetate phthalate.*

A specially designed apparatus was used for measuring the disintegration of these enteric coated medication units. These tablets were observed in artificial gastric fluid (at 37° C.) in which an oscillating motion was maintained simulating gastric peristaisis. The N. A. A. in these tablets began to diffuse through the coating within 15 minutes and was completely dissolved within an average of four hours.

Six diabetics over 50 years of age willing to cooperate were selected. They were all already on a 1600 calorie diet consisting of a daily ration of 150 grams carbohydrate, 60 grams protein, and 70 grams fat. At the start none of these subjects received insulin. Four of these were given daily doses of N. A. A. tablets from 42 to 77 days while continuing upon the 1600 calorie diet. In Table I is shown the results obtained on blood and urine sugar prior to, during and after N. A. A. treatment in these four cases. The other two cases were carried along for one week and showed no deviation from the results reported in the table. The urinary excretion of creatinine and creatine showed considerable increase for two weeks after treatment with N. A. A. in three out of these four subjects. After three weeks of this treatment, the urinary excretion of creatinine and creatine became lower than at the commencement of this experiment.

Although the results obtained with N. A. A. were far from encouraging, diphosphopyridine nucleotide (D. P. N.) together with N. A. A. was tried. In the two cases reported in Table 2, T. G. showed little response to insulin and J. S. was continued on a 1600 calorie diet (without insulin).

Our data does not confirm Neuwahl's experience. The use of D. P. N. produces some positive results, and indicates the need for more exploration. To that end further studies are being conducted at present using D. P. N. in combination with other substances.

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[a] The niacinamide used in these experiments was generously donated by Merck and Co., Rahway, N. J.

* We are thankful to Mr. Joseph L. Kanig and staff at Columbia University, College of Pharmacy for specially preparing these tablets and testing them.

TABLE 1

Initials	Sex	Age	Urine Sugar	Blood Sugar mg. %	Date	Remarks
R. R. (1)	♀	51	H. T.	251	6/11/49	1600 calorie diet
			1.0%	332	8/13	1600 calorie diet
			H. T.	240	10/15	Started 1000 mg. N. A. A. daily
			H. T.	249	10/29	Started 1000 mg. N. A. A. daily
			1.2	237	11/5	Increased N. A. A. to 2000 mg. daily
			1.2	244	11/12	
			H. T.	269	11/26	Discontinued N. A. A.
			H. T.	221	1/17/50	1600 calorie diet cont'd.
			H. T.	240	3/ 4	
			1.1	209	4/ 8	
E. G. (2)	♀	53	2.1%	307	5/ 4/49	1600 calorie diet
			H. T.	260	9/10	1600 calorie diet Started 2000 mg. N. A. A. daily
			Neg.	200	10/15	
			F. T.	251	10/22	
			H. T.	269	10/29	
			F. T.	296	11/26	Discontinued N. A. A. Given 20 units Insulin daily. 1600 calorie diet cont'd.
			Neg.	237	3/18/50	
			F. T.	280	6/3	

Initials	Sex	Age	Urine Sugar	Blood Sugar mg. %	Date	Remarks
B. W. (3)	♂	60	H. T.	233	8/23/49	1600 calorie diet
			—	—	10/15	1600 calorie diet Started 2000 mg. N. A. A. daily
			H. T.	223	10/29	
			H. T.	233	11/12	
			1.1%	311	11/26	Discontinued N. A. A. Given 10 units Insulin daily. 1600 calorie diet continued
			Neg.	172	12/24	
			H. T.	230	1/28/50	
I. S. (4)	♀	58	—	—	10/22/49	1600 calorie diet Started 1000 mg. N. A. A. daily
			1.6%	211	10/29	
			3.4%	239	11/19	
			1.2%	200	12/10	Discontinued N. A. A.
			3.4%	233	3/ 4/50	Diet continued
			2.8%	251	4/15	

TABLE 2

Initials	Sex	Age	Urine Sugar	Blood Sugar mg. %	Date	Remarks
T. G.	♀	51	4.2%	304	5/14/49	
			2.0	480	8/13	Started 45 units insulin daily
			4.0	335	12/17	45 units insulin cont'd. Started 1000 mg. N. A. A. tablets daily + 0.7 mg. D. P. N. once a wk. intramuscularly
			2.0	177	12/24	Reduced insulin to 40 units daily
			—	—	1/ 7/50	Given 1000 mg. N. A. A. daily in solution
			2.1	149	1/21	
			1.1	280	2/ 4	Started daily injection of D. P. N.
			H. T.	—	2/11	
			1.9	260	2/18	Discontinued D. P. N. and N. A. A.
			4.2	304	3/4	Started daily injection of 0.7 mg. D. P. N.
			1.0	209	3/11	Stopped D. P. N. but continued 40 units insulin
			3.2	272	7/1	

Initials	Sex	Age	Urine Sugar	Blood Sugar mg. %	Date	Remarks
J. S.	♂	61	1.1	203	4/30/49	1600 calorie diet
			H. T.	209	6/11	
			1.0	201	10/29	
			H. T.	197	12/24	Started 1000 mg. N. A. A. daily in solution + 0.7 mg. D. P. N. injected intramuscularly once a week
			H. T.	189	1/ 7/50	
			H. T.	—	1/14	
			F. T.	150	1/21	
			F. T.	150	2/ 4	
			H. T.	168	2/18	Discontinued N. A. A. and D. P. N. 1600 calorie diet cont'd.
			1.2	181	3/18	
			0.9	240	7/ 1	

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SELECTED ABSTRACTS

Local Terramcyin Therapy in Tuberculous Otitis Media. Titche, L. L. *U. S. A. F. Med. J. 3*:63 (1952). A patient hospitalized for recurrent pulmonary tuberculosis developed a discharge from his left ear. Penicillin was given parenterally and locally while waiting for a laboratory report. No benefit was derived from this therapy. The culture report revealed tubercular bacilli. Roentgenologic examination revealed an infected mastoid process. Local instillations of 0.1 Gm. of streptomycin were given daily but 4 weeks later the involvement had progressed. Then 50 mg. of terramycin in 1 cc. of distilled water was instilled locally into the ear daily. In about a month the ear was dry and negative to culture and the mastoid cells were clearing up.

The author pointed out that this single case was reported because prior literature reports on the use of terramycin in tuberculosis therapy had involved oral treatment, and not local treatment as in this case. These prior reports had indicated that terramycin was ineffective against the tubercle bacilli when given orally.

Treatment of Parkinsonism. Effron, A. S., *GP 4*:61 (1951). The solanaceous alkaloids, or combinations of these alkaloids, have been the drugs most used in the treatment of Parkinson's disease. Recently, the antihistaminic compounds have been investigated for their effectiveness in the treatment of the symptoms of this disease. The author studied the effect of Artane (trihexyphenidyl), a synthetic antispasmodic having certain atropine-like effects and two antihistaminics, Tagathen and Thephorin.

The study involved 45 unselected patients with Parkinson's disease, the majority of whom were of the postencephalitic type. In order to compare the different medications and combinations of them each patient was deprived of all medication until a base line had been established. Between each course of therapy with one of the medications or combinations the base line was again attained by the use of placebos made to look exactly like the medication. Artane and Tagathen were administered singly and then together and then Artane

and Bellabulgaria (belladonna alkaloids) and Artane and Thephorin were administered.

Tagathen alone had little effect on the symptoms of the disease. Artane alone brought benefit to approximately 73 per cent of the patients. Artane and Tagathen and Artane and Bellabulgaria brought only a slightly higher incidence of improvement than with Artane alone. However, the combination of Artane and Thephorin brought about improvement in 95.5 per cent of the cases and a higher incidence of those receiving marked improvement.

A few patients who had experienced side effects with Artane alone were better able to tolerate the combination with Thephorin. Rigidity was more rapidly and more effectively controlled than was tremor. However, tremor improved considerably in most cases. Gait usually improved along with the reduced rigidity. Speech was improved where there was impairment and excessive salivation and perspiration were diminished.

The initial dose of Artane was 1 mg. and of Thephorin 25 mg. This was gradually increased until, at the beginning of the 4th week, a maximum of 5mg. of Artane and 50 mg. of Thephorin, 4 times a day, was being given.

Terramycin in the Prophylaxis of Ophthalmia Neonatorum. O'Brien, Donough.- *The Lancet 1*:347 (1952). The author pointed out that the availability of the antibiotics now makes ophthalmia neonatorum no longer particularly difficult to treat and has markedly reduced the incidence of gonorrheal infections. Nevertheless, he stated that ophthalmia neonatorum is still of considerable nuisance and that, therefore, an attempt to reduce its incidence is decidedly worth-while.

Terramycin was given either in the form of eye drops or in an ointment. The eye drops were prepared by adding 25 mg. of crystalline terramycin hydrochloride to 62.5 mg. of sodium chloride and 25 mg. of crystalline sodium borate already sterilized. Before use, the salts were dissolved in sufficient sterile distilled water to provide a concentration of 5 mg. of terramycin per 100 cc. After the solution was made it was discarded after 48 hours if not used. The ointment was prepared as needed in a strength of 1 mg. of terramycin per 100 Gm. of a sterile petrolatum base and placed in eye-tip ointment tubes.

Female infants were used as controls. Immediately after birth the eyes were simply cleansed by wiping with small dry sterile gauze pads. The eyes of male infants were likewise cleansed and then either 2 drops of the solution or about 30 mg. of the ointment was instilled into each conjunctival sac. In all 254 infants received the drops and 270 received the ointment. A total of 523 infants served as controls. The incidence of infection ranged from 2.9 to 7.0 per cent in the groups. However, the difference between the treated and the untreated groups was not statistically significant. Therefore, the author concluded that terramycin in the concentration used is of no value in the prevention of ophthalmia neonatorum.

The Use of Terramycin in Infections in Infants and Children. Wolman, B. and Holzel, A. *Brit. Med. J.* No. 4755:419 (1952). Because of the wide antibacterial spectrum, the low toxicity, the rapid absorption from the gastro-intestinal tract, and the palatability by the oral route of administration terramycin seems to be particularly suited for pediatric use. The authors treated 66 infants and children with terramycin in the form of a cherry-mint elixir. The usual dosage employed was 50 mg. per pound of body weight per day, given in divided doses every six hours for a period of seven days.

Among 35 patients with pneumonia the temperature returned to normal within 24 hours in 23, within 48 hours in 7, and within 72 hours in 1. One patient with Friedlander's bronchopneumonia died. *Streptococcus viridans, S. haemolyticus,* Pneumococci, *Staphylococcus pyogenes,* and *Haemophilus influenzae* were isolated from the nasopharyngeal cultures of various patients as the predominant organism. Improvement was rapid and effective in 10 patients with upper respiratory tract infections, in 6 with tonsilitis, and in 3 with pyuria. Eleven of 12 newborn infants with purulent conjunctivitis responded rapidly to treatment. Treatment was administered in the form of an ophthalmic solution containing 25 mg. terramycin hydrochloride, 62.5 mg. sodium chloride, and 25 mg. sodium borate in 5 cc. of distilled water. The one infant that did not respond to terramycin responded to streptomycin. Two of the 3 patients with pneumonia who did not respond to terramycin responded to aureomycin.

There were no toxic reactions in this series of patients with the exception of a scarlatiniform rash which developed in 2 patients on the third day after the cessation of treatment.

BOOK REVIEWS

A Study of Antimetabolites. By D. W. Woolley, Member, The Rockefeller Institute for Medical Research. xiii + 269 pages. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1952. Price $5.00.

This scholarly attempt to systematize the present status of our knowledge concerning antimetabolites, a new subdivision of biochemistry, has been carefully planned and presented in a style worthy of the author whose scientific stature is well recognized. Dr. Woolley's own investigations have furnished him with considerable personal experience in this field which is rapidly becoming established as one of the most stimulating aspects of the mother discipline.

The subject is introduced with a brief historical outline and a summary of antimetabolitic phenomena. Then follows a discussion of the following topics: hypotheses concerning the mechanism of action of antimetabolites; the spectrum of their activity; their participation in physiological processes and as etiological agents in disease; their selectivity of action; their applications to chemotherapy, pharmacology, and biochemistry; the designing of antimetabolites; and practical suggestions for the synthesis and testing of antimetabolites.

The major criticisms of the book are its sparsity of illustrative material, the many inconsistencies in structural formulae, and the fact that the compilation was at least two years old when published. Nevertheless this book should be a part of the library of every investigator working in the biological sciences, particularly biochemists and pharmacologists. This volume is one of the first in its field and will be useful for many years.

ERIC W. MARTIN

Pharmaceutical Botany. By Heber W. Youngken. Seventh Edition, 1951. 548 illustrations, 753 pages. $7.00. The Blakiston Co., Philadelphia.

This is a handsome new edition of the standard text on pharmaceutical botany. The 23 chapters have been rearranged to approximate the usual sequence of a general botany text. As a result of the changes in sequence of chapters, the text proceeds gradually from the simpler

to the more advanced problems of botanical science. The chapters have been rewritten to include new material on plant physiology, plant anatomy, synthetic chemical growth regulators, plant hormones and vitamins. The chapter on classification includes both the traditional and the newer system of classification of the plant kingdom. Two new chapters are those on plant environment and metabolism. The appendices contain a treatise on the microscope and its use, and detailed directions for histological techniques. An extensive glossary, a classified list of reference works, and a 50 page index completes the book.

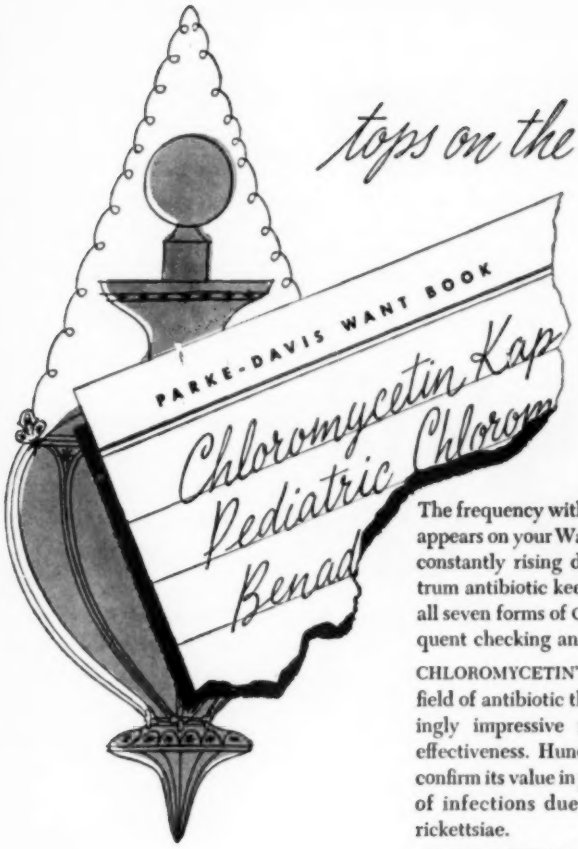
Pharmaceutical Botany by Youngken is the outstanding textbook of its type and is a "must" for students and teachers of pharmaceutical botany. In the new Seventh Edition the pharmaco-botanical material has been fully retained and augmented. However, the usefulness of the book is greatly increased over that of previous editions due to the inclusion of additional basic principles and material on general botany.

E. H. M.

Clark's Applied Pharmacology. By A. Wilson and H. O. Schild. viii Ed. 1952. xii + 691 pages. The Blakiston Company, Philadelphia.

The posthumous eighth edition of Clark's *Applied Pharmacology* has been thoroughly revised by A. Wilson and H. O. Schild, and the references to the U. S. P. were prepared with the aid of A. Osol from the Philadelphia College of Pharmacy and Science. The aim of the book is to present the fundamentals of pharmacology as applied to the art of therapeutics. Materia medica aspects are not emphasized. The authors consider the student who has not yet studied pathology and who needs a review of physiology. The individual sections are built up with masterful pedagogic skill—reviewing the physiological basis, the pathological implications, the pharmacodynamics, and the therapeutic applications of the drugs under discussion. Although covering a wide field, this book is relatively small in size, presenting the material in a clear, condensed form. Primarily designed for medical students, it will serve equally well the student of related sciences.

Julian L. Ambrus



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